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THE EFFECT OF DEFICIENCY AND EXCESS OF THYROID FUNCTION ON FORCED EPIDERMAL REGENERATION*

HERMANN PINKUS, M.D. AND ROSIE HUNTER

Removal of the horny layer of human epidermis by tape stripping is followed by a mitotic burst which replaces lost and damaged cells within a few days (1). This forced proliferation can be observed even in tissue culture by stripping the excised skin, as was shown by Reaven and Cox (2). The activation therefore does not depend on inflammation or other systemic factors, but appears to be due to an effect on the epidermal cells themselves. On the other hand, when we gave high oral doses of Vitamin A to volunteers for one month before stripping (3) we found suggestive evidence that the mitotic effort had a lower peak and was more prolonged. At the same time, the proportion of immature living cells to mature keratinized cells was shifted in favor of the former (4). It seems, therefore, that the stripping test gives information concerning epidermal proliferative potential under the homeostatic conditions prevalent in the tissue at the time of stripping. It may be considered a "tolerance" test analogous to other tolerance or loading tests by which we measure functional potential of various organs or tissues.

Thyroid hormone being one of the most potent regulators of tissue homeostasis, we decided to compare epidermal regeneration potential in myxedematous and hyperthyroid patients.

MATERIAL AND METHODS

Nine myxedematous and eleven hyperthyroid patients were studied immediately after hospital admission and before any therapy was instituted. Data on individual patients are shown in Table I. Scotch Tape® was applied and stripped off the volar skin of the forearms repeatedly according to the method described previously (1, 5), until a dry glistening surface was obtained. Two-millimeter punch biopsies were taken 24, 48, 72, and 96 hours later using local anesthesia with lidocain and were compared with control specimens obtained from normal skin of the same individuals. The tissues were fixed in formal-alcohol, embedded in paraffin, and vertical 8 micron sections were cut and stained with H&E. Interphase nuclei and mitoses were counted under oil immersion according to previously described methods.

RESULTS

Fig. 1 shows sections of unstripped epidermis (a and c) and of epidermis 24 hours after stripping (b and d). The atrophic and hyperkeratotic epidermis of the myxedematous patient (a) is in striking contrast to the turgid hyperthyroid epidermis (c). After 24 hours, we see absence of most of the horny layer and beginning hypertrophy of epidermal basal cells in both specimens. Fig. 2 compares 48, 72, and 96 hour specimens. While the proliferative changes are similar, the myxedematous epidermis never quite attains the thickenss and hyperplastic state of the hyperthyroid epidermis.

Counts of nucleated cells below the granular layer showed that the thinner myxedematous stratum Malpighii contains a slightly higher percentage of basal cells (Fig. 3) except in the 96 hour specimens. In previous work, we always expressed mitotic counts in percentages of "intermitotic" cells which were defined according to Cowdry as the sum of basal and prickle cells below the granular layer. Meanwhile, our own impression that practically all mitoses begin in the basal layer has been confirmed so convincingly by others (6) that it seems advisable to express mitotic counts as percentages of basal cells. Actually, the results of this and our earlier investigations are not affected significantly by this technical alteration.

Fig. 4 shows curves obtained by plotting mitoses expressed as percent of basal cells against time. Mean and highest and lowest values are shown. Mitotic counts are much

* From the Departments of Dermatology, Wayne State University College of Medicine, and Detroit General Hospital, Detroit, Michigan.
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higher in myxedematous skin, but there are wide individual variations. Individual counts are shown in Table II.

In order to obtain a clearer picture we decided to consider the "total mitotic effort" of each patient by adding mitotic counts obtained at 48, 72, and 96 hours. Total mitotic effort divided by 3 is then the "mean mitotic effort." The highest percentage of mitoses found at any time in each case is designated as "mitotic peak." Fig. 5 shows mean and high and low limits of these values. It is even more obvious that mitotic counts in the epidermis of severely myxedematous patients exceed those of hyperthyroid patients at all times.

TABLE I

I-131 uptake at 24 hours (normal range 15–50%)

Hypothyroid Patients					Hyperthyroid Patients				
No.	Sex	Race	Age	%	No.	Sex	Race	Age	%
1	F	W	45	1.5	1	F	C	70	53.0
2	M	W	67	2.5	2	M	C	46	79.0
3	M	W	72	20.0	3	F	C	42	82.0
4	F	W	47	3.0	4	F	C	20	78.0
5	M	W	80	1.5	5	F	C	43	90.0
6	M	C	55	1.0	6	F	C	25	59.0
7	F	W	69	11.0	7	F	W	76	84.0
8	F	C	70	3.0	8	M	C	35	79.0
9	F	W	46	12.0	9	F	C	25	73.0
					10	F	C	76	?
					11	F	C	62	75.0

DISCUSSION

We considered several explanations of this unforeseen result. It seemed possible that an atrophic epidermis would be stimulated more than a relatively active one. However, that assumption does not explain the high mitotic counts in control specimens. It is possible that bathing and cleaning procedures after hospital admission could have an effect similar to mild stripping in the indolent and neglected myxedematous patients. However, perhaps the most likely explanation is that in thyroid deficiency the mitotic process is slowed down along with other metabolic functions. Longer mitotic duration would give higher mitotic counts. That mitotic duration may vary has been demonstrated by Evenson (7) who could show that the so-called diurnal rhythm of mitotic activity in mouse epidermis actually is a rhythm of mitotic duration. Weinstein and Frost recently reported that mitotic duration is much reduced in psoriatic epidermis (8). When we re-drew our graph (Fig. 6) with the assumption that mitotic duration is doubled in the

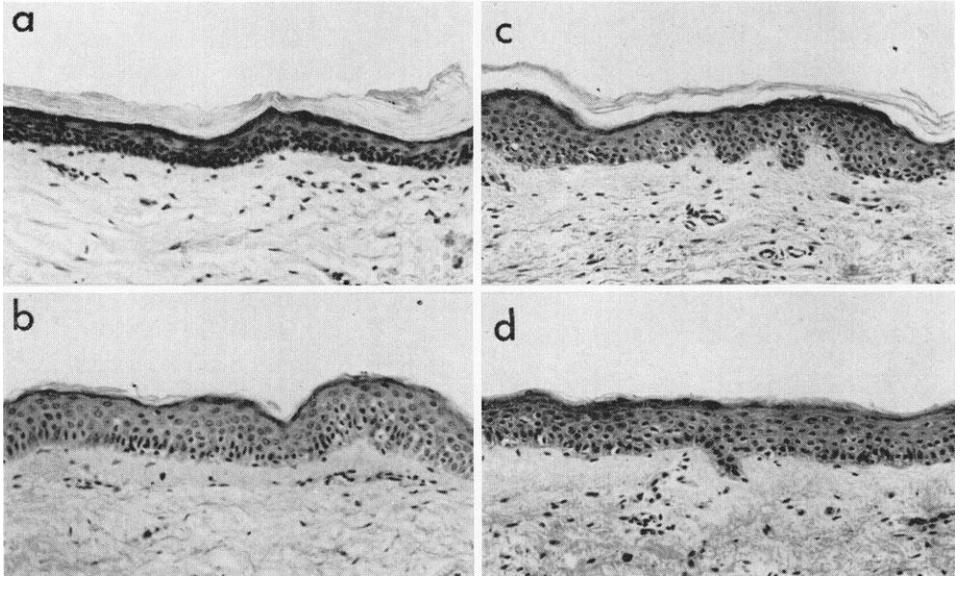

FIG. 1. Myxedematous (a, b) and hyperthyroid (c, d) skin before (a, c) and 24 hours after stripping (b, d). H&E, 135 ×.

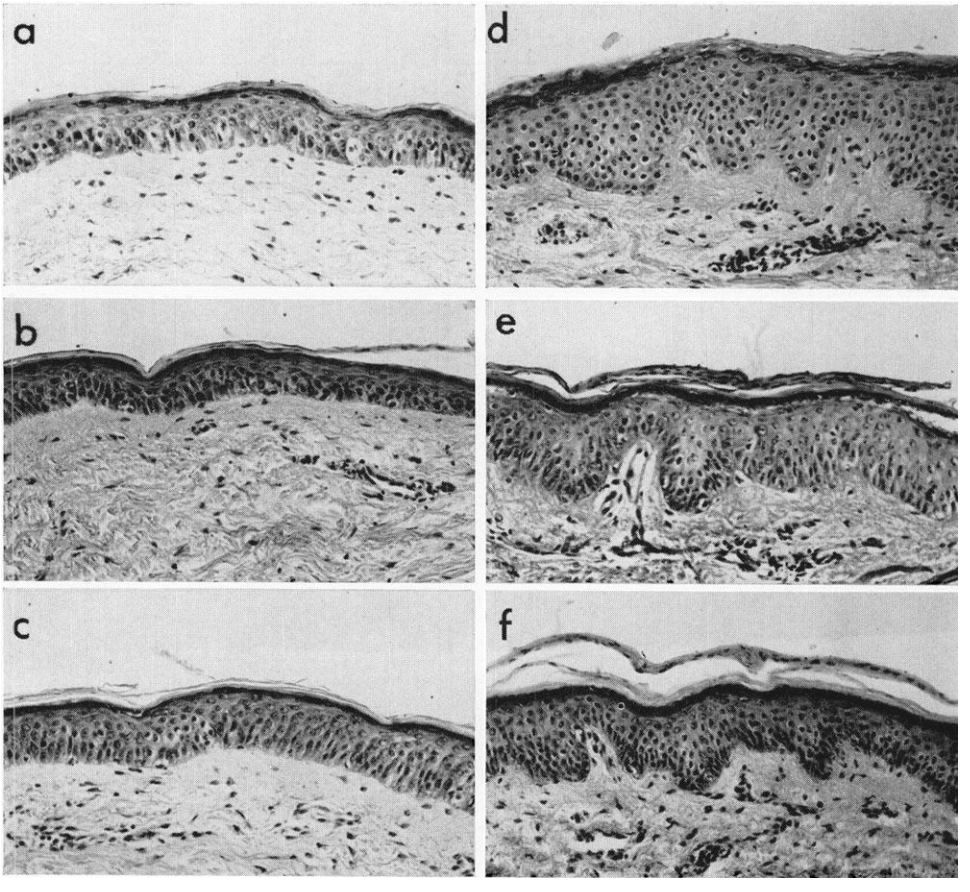

FIG. 2. Myxedematous (a, b, c) and hyperthyroid (d, e, f) skin at 48 hours (a, d), 72 hours (b, e), and 96 hours (c, f) after stripping. H&E, 135 ×.

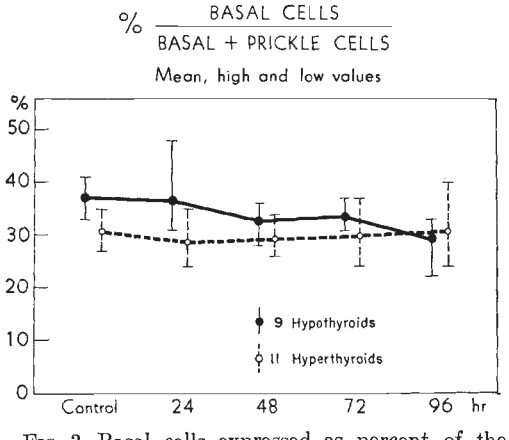

FIG. 3. Basal cells expressed as percent of the sum of basal and prickle cells below the granular or parakeratotic layer.

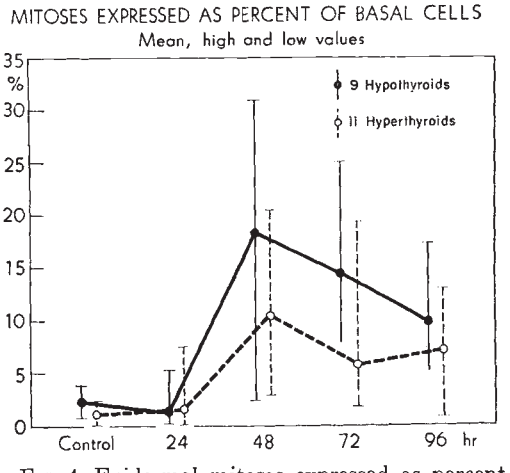

FIG. 4. Epidermal mitoses expressed as percent of basal cells in control skin and 24, 48, 72, and 96 hours after stripping. The horizontal bars indicate highest and lowest individual values in this and all following graphs.

TABLE II

Mitoses expressed as percentages of basal cells

Case No.	Age	Sex	Control	24 Hr.	48 Hr.	72 Hr.	96 Hr.	Mitotic peak	Mitotic total	Effort mean
					Hypothyroid					
1	45	F	0.9	0.2	2.3	16.5	11.0	16.5	29.8	9.9
2	67	M	3.7	0.7	31.0	8.0	9.0	31.0	48.0	16.0
3	72	M	0.9	0.9	14.0	17.1	—	17.1	31.1	15.6
4	47	F	0.8	0.8	9.5	7.8	5.1	9.5	22.4	7.5
5	80	M	2.5	3.6	27.0	17.3	17.3	27.0	61.6	20.5
6	55	M	1.0	0.3	26.3	8.1	7.0	26.3	41.4	13.8
7	69	F	6.8	2.9	22.5	25.0	7.9	25.0	55.4	18.5
8	70	F	3.9	—	21.5	11.1	8.1	21.5	40.7	13.6
9	46	F	3.6	5.3	10.7	18.5	14.0	18.5	43.2	14.4
					Hyperthyroid					
1	70	F	0.5	1.5	4.8	2.6	13.0	13.0	20.4	6.8
2	46	M	1.2	1.9	16.1	9.9	10.8	16.1	36.8	12.3
3	42	F	2.1	0.1	12.4	4.5	2.3	12.4	19.2	6.4
4	20	F	0.3	0.8	2.9	2.2	10.1	10.1	15.2	5.1
5	43	F	0.1	7.5	6.2	6.2	9.6	9.6	22.0	7.3
6	25	F	0.4	1.6	12.9	2.0	0.8	12.9	15.7	5.2
7	76	F	0.2	0.6	3.0	19.3	1.8	19.3	24.1	8.0
8	35	M	1.6	1.5	9.4	4.3	11.6	11.6	25.3	8.4
9	25	F	2.3	0.6	20.5	1.8	9.0	20.5	31.3	10.4
10	76	F	1.5	0.7	7.3	4.7	4.7	7.3	16.7	5.6
11	62	F	1.5	2.0	17.6	3.9	4.7	17.6	26.2	8.7

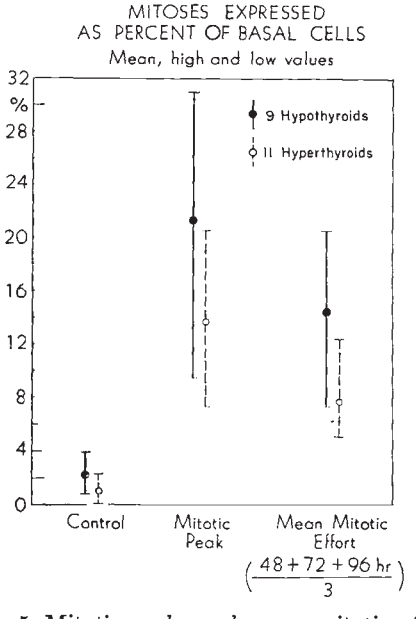

FIG. 5. Mitotic peaks and mean mitotic effort compared with control values.

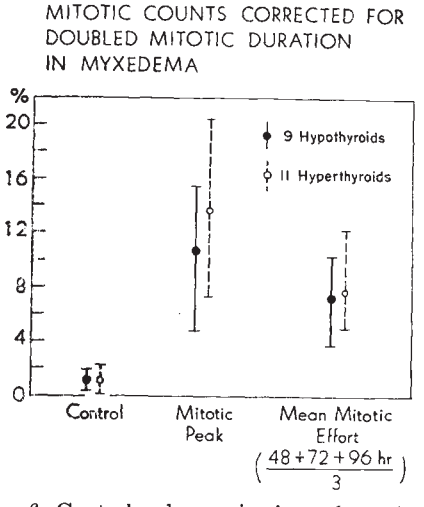

FIG. 6. Control values, mitotic peaks and mean mitotic effort under the assumption that mitotic duration in myxedematous epidermis is twice that of hyperthyroid epidermis. Compare with Fig. 4.

myxedematous patient, all the mitotic values fall in line. Further investigation using radioactive thymidine will have to confirm or rule out this assumption and to ascertain just what the duration of mitosis is in hypothyroidism and hyperthyroidism.

SUMMARY

Epidermis of severely myxedematous patients consistently shows higher mitotic counts than that of hyperthyroid individuals. Epidermal proliferative potential after tape stripping also appears to be much higher when judged by mitotic counts. We propose that these phenomena are caused by longer mitotic duration in thyroid deficiency rather than by higher mitotic activity.

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